Attorney's Docket No. 038151/203996 PATENT



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re: Thomas N. Masters
Appl. No.: 10/088,538
Filed: June 10, 2002
For: SOLUTION FOR THE PRESERVATION OF HEARTS

Confirmation No.: 6926
Group Art Unit: 1617
Examiner: Gregory W. Mitchell

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Applicant requests review of the final rejection in the above-identified application pursuant to the pilot program stated in the OG Notice of July 12, 2005. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).

Respectfully submitted,

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**CERTIFICATE OF MAILING**

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on ~~June 16~~ Nov. 11, 2005.

Janet F. Sherrill

REMARKS

The Examiner has failed to establish a *prima facie* case of obviousness. Please refer to the responses filed on June 20, 2005 and January 18, 2005 and the detailed arguments presented thereon regarding the deficiencies in the rejection. The Examiner's response to these arguments, as set forth in the Final Rejection of September 9, 2005, does not cure these deficiencies.

***The Invention***

The Applicant has developed a new medicament and a method of using the medicament for preserving and storing a heart awaiting transplantation. That the medicament performs its intended function, that of preserving a heart awaiting transplantation, is abundantly clear from the experiment disclosed in the specification at pages 10-14, and shown in the results set forth in FIGS. 2-7. These results show that ATP and CP concentrations were remarkably reduced during preservation with cyclosporin A after 18 hours of preservation.

***Claim Rejection – 35 U.S.C. § 103***

Claims 6-7 and 9-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Raymond, U.S. Patent No. 5,693,462, in view of Massoudy *et al.* (J. Mol. Cell. Cardiol. 29, 535-544).

***The Prior Art Does Not Teach All of the Claimed Limitations***

As recognized by the Examiner, the Raymond reference does not teach or suggest the utilization of cyclosporin A in the composition or methods disclosed therein. Moreover, neither Raymond, nor any of the other the prior art of record, teaches or suggests this concept which is at the center of applicant's invention.

The Examiner's position is that the Raymond patent teaches a preservation solution for preserving and storing organs comprising:

(a) an isotonic solution;

(b) an amiloride-containing compound;

(c) adenosine; and

(d) water.

The active ingredients in the Raymond solution that materially affect its properties are the amiloride-containing compound and adenosine. Raymond uses the amiloride-containing compound as one of the "active ingredients in the preservation solution" to inhibit Na+ - H+ exchange. *Col. 5, lines 32-35.* The other "active and material ingredient" is adenosine.

On the other hand, the active and material ingredient in the preservation solution of the claimed invention is cyclosporin A. The Examiner acknowledges that Raymond does not specifically teach the utilization of cyclosporin A in the composition or methods disclosed therein. The method of Raymond includes a medicament that requires the use of an amiloride-containing compound and adenosine. These products are excluded in the claims of the subject invention by the use of the limiting transitional phrase -- consisting essentially of --.

The Examiner states that Massoudy *et al.* teaches that cyclosporin A acts as a cardio protective agent in ischemia and reperfusion. According to the Examiner, Cyclosporin A, in concentrations of 0.8 μM in Krebs-Henseleit buffer, was shown to significantly prevent the loss of post-ischemic cardiac function (p. 537, col. 1, second full paragraph; p. 539, col. 2, first paragraph). The Examiner then argues that

> One would have been *motivated* to add cyclosporin A of Massoudy *et al.* to the composition of Raymond because of an *expectation of success* in improving the cardio protective characteristics thereof. *Office Action dated June 20, 2005 at page 3.*

The Examiner points to page 537 of Massoudy *et al.* to show that cyclosporin A is used to concentrations of 0.08 μM and 0.8 μM which is the effective plasma level required in patients after heart transplantation. It should be pointed out with respect to Claims 6 and 11 of the present application that the amount of cyclosporin A is present in an amount of about 2.5 μM to about 10 μM per liter of solution. The lower level CSA used in the present invention is **at least three times** the amount of CSA disclosed in Massoudy *et al.* The reason for that is the heart is being preserved prior to transplantation. Thus, the effects of cyclosporin A would be expected to be very different.

Method Claim 6 has been amended to limit the claim to "consisting essentially of". Claims 7 and 9-10 depend from Claim 6. Claims 11-14 are directed to a medicament and are cast in "consisting essentially of" terms. It is well-settled that the transitional phrase "consisting essentially of" only opens the claims to the inclusion of ingredients that would not materially

affect the *basic* and *novel* characteristic of the claim. *In re Herz*, 453 F.2d 549, 190 USPQ 461, 463 (CCPA 1976); M.P.E.P. §2111.03 [R-2].

Even if Raymond and Massoudy *et al.* were to be combined, that they would not teach the claimed invention because the medicament and method of Raymond would necessarily include the use of an amiloride-containing compound and adenosine. Also, the amount of CSA taught in Massoudy *et al.* is at least 1/3 lower that that claimed.

It is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness. It is submitted that the Examiner must, *inter alia*, show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Thrift*, 63 USPQ.2d 2002, 2006 (Fed. Cir. 2002). The factual inquiry of whether to combine references must be thorough in searching and cannot be performed wily nilly through the use of hindsight. Thus, the reason for there being some teaching motivation or suggestion to select and combine portions of the references relied upon as evidence of obviousness in such manner as the claims. Furthermore, deficiencies in the cited references cannot be remedied by general conclusions about what is "basic knowledge". *In re Sang Su Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002).

***There Is No Suggestion Or Motivation To Combine Massoudy et al. With Raymond***

A 15 minute interruption of blood flow and reperfusion which Massoudy *et al.* describe in their article, has little or no relationship to the claimed method for blocking apoptosis during preserving and storing a heart. The major alteration in the canine preserved heart at 18 hours is the appearance of apoptotic cells that indicate a programmed cell death and also the reason that permanent damage occurs in the myocardium. This kind of damage is not seen in the Massoudy *et al.* process. Actually, the inventors did not find apoptotic cells in the solutions used in the claimed method until after 12 hours of preservation. Irreversible damage occurs when apoptotic cells are detected at 18 hours. The unique finding is that cyclosporine A prevents apoptosis and therefore prolongs the preservation time for the heart.

Preventing apoptosis has nothing to do with the findings that Massoudy *et al.* mention at this stage with a nitric oxide-dependent mechanism impeded by endothelin. Massoudy *et al.*

disclose a reperfusion solution in which cyclosporin A is present in an amount of only 0.8 μM per liter. The Massoudy *et al.* article does not teach use of Raymond's amiloride in any type of solution whatsoever in the claimed amount. Massoudy *et al.* deal with a completely different technical problem over the present application, which is to minimize the reperfusion entry following the ischemic event. The teachings of Massoudy *et al.* show that the level of venus NO recovers faster after the ischemic episode and remains stable if the heart is perfused with the isotonic solution comprising cyclosporin A. Massoudy *et al.* is silent about the effects on an isolated heart preserved in the isotonic solutions disclosed in Massoudy *et al.* Thus, departing from Raymond as the primary reference, there is no particular reason for which one skilled in the art would turn to Massoudy *et al.* because Massoudy does not suggest that the isotonic solution therein disclosed would be particularly suited for solutions for preserving and storing a heart awaiting transplantation.

Therefore, the proposed combination of the Raymond and Massoudy *et al.* references lacks the necessary motivation required to establish a *prima facie* case of obviousness.

***No Expectation of Success***

Because of the fundamental differences between an amiloride-containing compound and adenosine on the one hand and CSA on the other, as outlined above, persons of skill in the art who are familiar with both would not consider the substituting one for the other. The preservation selection of Raymond does not contemplate blocking apoptosis during preserving and storing a heart. Furthermore, the fact that a CSA-containing agent may have been successfully used in reperfusion treatment, as taught by Massoudy *et al.*, says nothing about whether this could be successfully implemented to block apoptosis using an entirely different solution. The Examiner's justification for this combination of solutions that both Raymond and Massoudy *et al.* improve "the cardio protective characteristics" is inadequate and not grounded in fact or in law. For these reasons, the rejection also lacks the second requisite of establishing a *prima facie* case of obviousness.

***The use of hindsight is improper***

The Raymond and Massoudy *et al.* references themselves contain no specific teachings that would incite someone to modify the Raymond solution to block apoptosis. Applicant has

shown above that the person of ordinary skill in the art would not, either from the reference itself or from the knowledge generally available to one of ordinary skill, be motivated to make the claimed modification, and moreover, this person of ordinary skill would have no reasonable expectation of success.

Assuming that some reasonable motivation existed for modifying the Raymond method and solution in light in the Massoudy *et al.* teachings, this modification should lead to placing Massoudy *et al.*'s CSA into the solution of Raymond containing an amiloride-containing compound and adenosine. However, in order to arrive at applicant's claimed invention, it is necessary to take Massoudy *et al.*'s specific teaching with respect to CSA and to apply it to an entirely different solution at an entirely different level of CSA than taught.

From the foregoing, it should be evident that a hindsight reliance upon applicant's own disclosure is the only conceivable basis why one would combine the Raymond and Massoudy *et al.* references in the manner set forth in the rejection. This is not a proper basis for an obviousness rejection.

***Conclusion***

Applicant has clearly shown that the requirements for establishing a *prime facie* case of obviousness under 35 U.S.C. §103 have not been met. Accordingly, the obviousness rejection should be withdrawn.